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Myocardial metbolism in heart failure: Purinergic signalling and other metabolic concepts

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Abstract

Despite significant therapeutic advances in heart failure (HF) therapy, the morbidity and mortality associated with this disease remains unacceptably high. The concept of metabolic dysfunction as an important underlying mechanism in HF is well established.

Cardiac function is inextricably linked to metabolism, with dysregulation of cardiac metabolism pathways implicated in a range of cardiac complications, including HF. Modulation of cardiac metabolism has therefore become an attractive clinical target. Cardiac metabolism is based on the integration of adenosine triphosphate (ATP) production and utilization pathways. ATP itself impacts the heart not only by providing energy, but also represents a central element in the purinergic signaling pathway, which has received considerable attention in recent years. Furthermore, novel drugs that have received interest in HF include angiotensin receptor blocker-neprilysin inhibitor (ARNi) and sodium glucose cotransporter 2 (SGLT-2) inhibitors, whose favorable cardiovascular profile has been at least partly attributed to their effects on metabolism. This review, describes the major metabolic pathways and concepts of the healthy heart (including fatty acid oxidation, glycolysis, Krebs cycle, Randle cycle, and purinergic signaling) and their dysregulation in the progression to HF (including ketone and amino acid metabolism). The cardiac implications of HF comorbidities, including metabolic syndrome, diabetes mellitus and cachexia are also discussed. Finally, the impact of current HF and diabetes therapies on cardiac metabolism pathways and the relevance of this knowledge for current clinical practice is discussed. Targeting cardiac metabolism may have utility for the future treatment of patients with HF, complementing current approaches.

Keywords (5): cardiac metabolism; heart failure; insulin resistance; metabolic therapy; purinergic signaling

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Abbreviations

ADHF acute decompensated heart failure

ANP atrial natriuretic peptide

ARNi angiotensin receptor blocker-neprilysin inhibitor

ATP adenosine triphosphate

BCAA branched chain amino acid

hCPT-1 carnitine palmitoyltransferase-1

CHF chronic heart failure

CV cardiovascular

DM diabetes mellitus

HF heart failure

HFrEF HF with reduced ejection fraction

FAO fatty acid oxidation

FA fatty acids

FFA free FA

GLP-1RA glucagon-like peptide-1 receptor agonist

IR insulin resistance

LVEF left ventricular ejection fraction

MetS metabolic syndrome

MI myocardial infarction

NPs natriuretic peptides

NYHA New York Heart Association

PDH pyruvate dehydrogenase

PFox partial fatty-acid oxidation

PPARs peroxisome proliferator-activated receptor agonists

RAAS renin–angiotensin–aldosterone system

SGLT-2 sodium glucose cotransporter-2

TCA tricarboxylic acid

TZDs thiazolidinediones

TMZ trimetazidine

1. INTRODUCTION

Heart failure (HF) is associated with a significant health burden with an estimated prevalence of 62 million patients worldwide(Benjamin, et al., 2017). Despite recent advances in HF therapies, the 5-year mortality rate continues to increase (Benjamin, et al., 2017). Current therapeutic approaches for HF target the neurohumoral systems and include the renin angiotensin aldosterone system and/or the β- adrenergic receptor signaling pathway, mineralocorticoid receptor antagonists, inotropes, diuretics, and mechanical devices (Ponikowski, et al., 2016). However, they do not sufficiently address the 'metabolic nature' of the heart.

Metabolic failure is considered to play a central role in the pathogenesis of HF (Neubauer, 2007). There is growing evidence that patients with HF exhibit disturbances in myocardial energy substrate metabolism, resulting in the progression and worsening of disease (Bertero & Maack, 2018; Stanley, Recchia, & Lopaschuk, 2005). Moreover, the role of adenosine triphosphate (ATP) as an extracellular signaling molecule in cardiovascular (CV) pathophysiology and its therapeutic potential in cardiac diseases have invoked significant interest recently and are discussed in a number of detailed reviews (Burnstock, 2006, 2007a, 2017).

Novel metabolic therapies to target cardiac metabolism have the potential to improve patient outcomes (Greene, et al., 2016; Wende, Brahma, McGinnis, & Young, 2017). This review aims to discuss the pivotal role of cardiac metabolism at all stages of HF (early, mid and advanced), the role of purine nucleosides and nucleotides as extracellular signaling molecules in the disease, and the effects of therapies approved for the treatment of HF (or associated co-morbidities) on cardiac metabolism, including its relevance for clinical practice. Finally, the concept of 'resetting' metabolic pathways as an important therapeutic option in HF is discussed.

2. CARDIAC METABOLISM IN HEALTH AND DISEASE

2.1 Metabolic pathways in the healthy heart

The normal adult heart obtains 60–100% of its ATP supply from fatty acid oxidation (FAO) (Stanley, Lopaschuk, Hall, & McCormack, 1997; Wisneski, Stanley, Neese, & Gertz, 1990). Mitochondrial oxidation of fatty acids (FAs) consumes more O_2 per molecule of ATP produced than most other sources of fuel, making FAs the less efficient substrate for energy production (Lopaschuk, Ussher, Folmes, Jaswal, & Stanley, 2010). Glucose metabolism exhibits a greater fuel efficiency, providing 40% more ATP per O_2 molecule. FAs are thus the dominant substrates for energy production in the unstressed heart, while glucose may become the favorable substrate in high-energy demand conditions (Depre, Vanoverschelde, & Taegtmeyer, 1999; Rosano, Fini, Caminiti, & Barbaro, 2008; Stanley, et al., 2005; Witteles & Fowler, 2008).

While glucose metabolism has a greater capacity to generate ATP, glycolysis accounts for just 5% of the ATP produced in the normal oxygenated heart (Abozguia, Shivu, Ahmed, Phan, & Frenneaux, 2009). *In vitro* and *in vivo* studies have demonstrated that glucose metabolism is inhibited by FAO and is dependent on the dietary state and physical activity of the body (Randle, Garland, Hales, & Newsholme, 1963; Randle, Newsholme, & Garland, 1964). This reciprocal relationship between FAs and glucose for oxidative metabolism was originally described by Randle *et al.* in 1963 (Randle, et al., 1963).

The common end product, acetyl coenzyme A (acetyl-CoA), produced from FAO or from the glycolytic pathway, is transferred into the citric acid cycle (also known as the tricarboxylic acid [TCA] cycle or the Krebs cycle) (Kantor, Lopaschuk, & Opie, 2001). Acetyl-CoA in the Krebs

cycle generates one molecule of ATP *via* substrate phosphorylation and the formation of reducing equivalents – three molecules of nicotinamide adenine dinucleotide (NADH) and one molecule of FADH2 (Berg, Tymoczko, & Stryer, 2002).

The metabolic flexibility of the heart is demonstrated by its ability to utilize energy substrates based on their availability and complex regulatory mechanisms (Kolwicz, Purohit, & Tian, 2013).

2.2 Shift of metabolic pathways in the progression of heart failure

Altered energetics plays a key role in the pathophysiology of the failing heart, which switches from FA utilization to oxygen-sparing carbohydrate metabolism for energy production (Bedi, et al., 2016) (Figure 1). Chronic HF (CHF) is associated with abnormalities in skeletal muscle metabolism that affect exercise capacity and contributes to insulin resistance (IR) (Jordan, et al., 2016). The metabolic alterations in cardiomyocytes depends on the stages of HF (early, mid or advanced) (Chandler, et al., 2004). Most studies show that FAO is unchanged or only slightly elevated in the early stages of HF(Chandler, et al., 2004; Stanley, et al., 2005). However, in advanced- or end-stage decompensated HF, there is a down-regulation in FAO enzyme expression, and FA utilization is decreased (Chandler, et al., 2004; Stanley, et al., 2005). Glucose utilization is typically increased in the early stages of HF (in the hypertrophied heart) and is mainly characterized by an increase in glucose uptake and glycolysis as a result of reduced oxidative metabolism (Allard, Schonekess, Henning, English, & Lopaschuk, 1994; Nascimben, et al., 2004). This increase in glucose metabolism could be due to alterations in the regulation of carbohydrate utilization pathways secondary to FAO suppression and/or upregulation of the anaplerotic pathway (Pound, et al., 2009; Sorokina, et al., 2007). In contrast, in advanced HF or

HF with type 2 diabetes, IR develops in the myocardium, resulting in decreased glucose metabolism (Kalsi, et al., 1999; Razeghi, et al., 2001; Taylor, et al., 2001). This shift from FAO to glucose metabolism is considered to be part of the 'foetal reprogramming' hallmark of cardiac hypertrophy and HF (Razeghi, et al., 2001). Gene expression profiling demonstrated early and sustained down-regulation of metabolic gene classes in HF (Rowell, Koitabashi, Kass, & Barth, 2014). A number of studies have demonstrated that the failing heart exhibits decreased expression and activity of enzymes involved in mitochondrial FAO (Iemitsu, et al., 2002; Osorio, et al., 2002). The reduced glucose oxidation seen in advanced HF is attributed, at least in part, to mitochondrial dysfunction. Functional blockade of the pyruvate dehydrogenase (PDH) complex, the rate- limiting step in glucose oxidation, is also thought to play a major role in this process (Doehner, Frenneaux, & Anker, 2014).

In addition to myocardial metabolism of glucose and fatty acids, the heart is also capable of oxidising a range of other substrates including ketone bodies, lactate and amino acids (Kolwicz, Airhart, & Tian, 2016). Ketone bodies compete with other substrates in the heart, especially FA, to be used as fuel. This is particularly significant in the hypertrophied and failing heart, wherein there is down-regulation of FAO gene expression (Tian & Barger, 2006) and increased blood ketone bodies (Lommi, et al., 1996). The increase in ketone bodies is proportionate to the level of cardiac dysfunction and neurohumoral activation (Lommi, et al., 1996). IR and cardiac cachexia are common features of advanced HF, which also increases the likelihood of ketone production and cardiac ketone utilisation (Schugar, et al., 2014).

The shift of energy metabolism to ketone body metabolism has been shown to be an efficient alternative avenue for oxidative ATP production (Aubert, et al., 2016). Ketone bodies, especially the principal ketone body D-β-hydroxybutyrate, have been proposed to act as a "superfuel", producing more energy than FA or glucose (Aubert, et al., 2016; Cahill & Veech, 2003; Sato, et al., 1995). This shift to ketone body metabolism is supported by a further case-control study, that evaluated the metabolic signature in the human non-diabetic failing heart (Bedi, et al., 2016). This study showed that the metabolic and genetic profile characteristic of ketone oxidation was present in failing hearts only, suggesting that ketone utilization is a late event in HF. It has been suggested that the failing heart relies on ketone metabolism when other substrate metabolism pathways begin to shut down (Bedi, et al., 2016; Taegtmeyer, et al., 2016). These observations are supported by studies in advanced HF patients, which demonstrated that the use of circulating ketones was reduced by 50% in skeletal muscle, but was preserved in cardiac tissue (Janardhan, Chen, & Crawford, 2011). In contrast, a more recent animal study reported that increased levels of ketone bodies impairs α-ketoglutarate dehydrogenase activity and blocks the Krebs cycle, subsequently resulting in contractile dysfunction (Karlstaedt, et al., 2016). In cardiomyocytes, ketone bodies cause concurrent inhibition of glucose and FAO, thereby impairing myocardial energy supply (Taegtmeyer, 1994). Furthermore, the O_2 consumed for ATP production during ketone metabolism is more efficient than FA, but less than that of glucose. However, more energy is derived from β-hydroxybutyrate versus glucose due to β-hydroxybutyrate being more reduced (Mudaliar, Alloju, & Henry, 2016). Interestingly, when β-hydroxybutyrate is infused in healthy volunteers to reach very high physiological levels, it is oxidized at the expense of glucose. Moreover, myocardial blood flow and heart rate also increase with the infusion of β-hydroxybutyrate, (Gormsen, et al., 2017), a phenomenon previously also observed for the

kidney, brain and forearm (Fioretto, et al., 1987; Hasselbalch, et al., 1996; Walker, Fulcher, Marsiaj, Orskov, & Alberti, 1991).

While these studies point to an important role of ketone bodies in cardiac metabolism and HF, it remains unclear whether ketone body metabolism is adaptive or maladaptive in heart failure. Targeted deletion of succinyl CoA-3-oxoacid CoA transferase (an enzyme essential for terminal oxidation of ketone bodies) in cardiomyocytes of mouse models of HF suggests that inability to oxidize ketones may predispose the heart to metabolic reprograming contributing to pathological remodeling following pressure overload (Schugar, et al., 2014). It has been suggested that myocardial ketone oxidation is a metabolic adaptation in the failing heart (Bedi, et al., 2016). Preference of ketone bodies over FA and glucose for oxidation to provide energy may not only improve cardiac function but also enhance cardiac efficiency (Ferrannini, Mark, & Mayoux, 2016). Although it would appear that ketone bodies have a positive effect on cardiac function, further studies are needed to clarify the long-term effects of ketone metabolism in patients with HF.

Perturbations in amino acid availablity and metabolism have also been observed in HF (Wende, et al., 2017). Accumulation of branched chain aminoacids (BCAA; including isoleucine, valine and the ketogenic aminoacid leucine) and their corresponding branched chain α-keto acid (BCKA) derivatives due to defective catabolism has emerged as one of the hallmark signatures of the metabolic changes in failing heart (Sun, et al., 2016; W. Wang, et al., 2016; Wende, et al., 2017). Elevated levels of BCKA may have a detrimental effect on cardiomyocytes due to cytotoxicity resulting from mitochondrial dysfunction and oxidative stress (Sun, et al., 2016). The accumulation of BCKAs has been attributed to transcriptional repression of subunits of the

BCKA dehydrogenase, a key enzyme involved in subsequent catabolism of BCKAs. These findings are further supported by the observation that pharmacolgical activation of BCKA dehyrdogenase prevents BCKA accumulation and improves cardiac function (Sun, et al., 2016). In addition to being potential sources of energy, BCAAs are also essentail for de novo protein synthesis and function as signaling molecules in various metabolic and growth pathways. For example, by activating mTOR, BCAAs (especailly lysine) may regulate diverse cellular processes like protein synthesis, autophagy and insulin signalling therby affecting glucose and FA metabolism, and muscle anabolism (Sun, et al., 2016; Wende, et al., 2017).

2.3 Purinergic signaling in HF

Purinergic signaling (ATP acting as extracellular signaling molecule) is mediated by purine receptors that are expressed in all cells of the heart and blood vessels including erythrocytes, leukocytes, and platelets (Burnstock, 2017; Burnstock & Knight, 2004; Burnstock & Pelleg, 2015). There are four subtypes of P1 G protein-coupled receptors (GPCR) (A_1, A_{2A}, A_{2B}, and A_3), seven P2X ($_{1–7}$) subtypes of ion channel receptors and eight subtypes P2Y GPCRs ($P2Y_{1/2/4/6/11/12/13/14}$) (Burnstock, 2007b; Ralevic & Burnstock, 1998). They mediate actions on the heart which are described in original publications (Burnstock & Ralevic, 2014; Givertz, 2009). The heart is controlled by the sympathetic, parasympathetic, and sensory nervous systems, which utilize ATP as a co-transmitter. Cardiac expression of purine receptors is increased in CHF patients (Hou, et al., 1999), with a resultant accumulation of adenosine in plasma (Funaya, et al., 1997). Furthermore, adenosine therapy has demonstrated cardioprotective effects in CHF patients, which are mediated through A_1 and A_3 receptors (Dougherty, Barucha, Schofield, Jacobson, & Liang, 1998; Liang & Jacobson, 1998).

Accumulating evidence supports the role of purinergic signaling in cardiac pathophysiology. An up-regulation of $P2X_1$ and $P2Y_2$ receptor mRNA was reported in the heart of a rat model of congestive HF (Hou, et al., 1999). Increased expression of $P2X_1$ receptors has similarly been reported in the atria of patiens suffering from dilated cardiomyopathy (Berry, Barden, Balcar, Keogh, & dos Remedios, 1999). Early *in-vivo* studies have shown that regulated over-expression of A_1 receptors leads to adverse ventricular remodeling. (Funakoshi, et al., 2006). This finding is in contrast to more recent data, indicating that adenosine accumulation may be cardioprotective in heart failure. Adenosine A_1 receptor activation attenuated cardiac hypertrophy in rat neonatal cardiac myocytes (Chuo, et al., 2016). Partial adenosine A1 agonism has demonstrated promise as a treatment for heart failure, with the potential to enhance cardiac metabolism, calcium homeostasis, cardiac structure and function, and patient outcomes, when combined with standard therapies (Greene, et al., 2016).

An association of purinergic signalling with cardiac energy metabolism has also been demonstrated, with animal studies showing that adenosine (an A1 receptor agonist) altered glucose metabolism and tended to decrease acidosis and calcium overload, exerting a cardioprotective effect. (Finegan, Lopaschuk, Coulson, & Clanachan, 1993; Fraser, Lopaschuk, & Clanachan, 1999; Puhl, et al., 2016). Adenosine inhibits adenyl cyclase and reduces intracellular levels of cyclic adenosine monophosphate (cAMP) (Akbar, Okajima, Tomura, Shimegi, & Kondo, 1994; Fredholm, AP, Jacobson, Klotz, & Linden, 2001; D. Wang & Belardinelli, 1994), subsequently leading to reduced sympathetic nervous system activation and increased release of atrial natriuretic peptide (ANP) (Schutte, Burgdorf, Richardt, & Kurz, 2006;

Yuan, Cao, Han, Kim, & Kim, 2005). Under hypoxic conditions, adenosine activates protein kinase C and improves mitochondrial function, by modulating mitochondrial sensitive potassium (mKATP) channels (Xiang, et al., 2010).

HF is characterized by volume overload, a condition that is particularly relevant for the effect of adenosine on the renal systems. Renal dysfunction is a major co-morbidity of HF, with about half of patients with CHF and two-thirds of patients with acute HF (AHF) presenting with associated cardiorenal syndrome (CRS) (Ronco, Haapio, House, Anavekar, & Bellomo, 2008). Adenosine has multiple, complex effects on the kidney, including vasoconstriction of afferent renal arterioles, sodium reabsorption in the proximal tubules and enhanced tubuloglomerular feedback (TGF) in the macula densa (Vallon, Muhlbauer, & Osswald, 2006). CHF is characterized by an increased accumulation of endogenous adenosine in plasma (Funaya, et al., 1997; Vallon, Miracle, & Thomson, 2008). In the kidney, adenosine can induce both vasoconstriction *via* the A_1 receptor (in the outer cortex) and vasodilation *via* the A_2 receptor (in the deep cortex and medulla) (Vallon, et al., 2008). The effect of adenosine on TGF plays a key role in the progression of the disease (Burnstock & Pelleg, 2015; Givertz, 2009). Increased renal adenosine levels mediate A_1 receptor activation and causes fluid retention by stimulating NaCl and fluid reabsorption in the proximal tubule (Vallon, et al., 2008). The net effect of these is fluid overload and decreased glomerular filtration rate (GFR).

2.4 Cardiac implications of co-morbidities

Metabolic syndrome: Metabolic syndrome (MetS) refers to a cluster of risk factors that can lead to heart disease, including obesity, dyslipidemia, elevated blood pressure and glucose

intolerance/IR.(American Heart Association, 2016; Hanefeld, Pistrosch, Bornstein, & Birkenfeld, 2016). Alterations in substrate availability/utilization and impairment in transcriptional regulation of oxidation pathways is often noted in MetS (Ilkun & Boudina, 2013). IR-mediated impairment of glucose transport leads to enhanced long-chain FA uptake through relocation of the FA transporter CD36 to the sarcolemma (Ouwens, et al., 2007) and increased mitochondrial carnitine palmitoyltransferase-1 (CPT-1) activity (Menard, et al., 2010).

There is mounting evidence to support the role for increased FA levels (as seen in MetS and diabetes mellitus [DM]) in mitochondrial oxidative dysfunction. The mechanism promotes cardiac lipotoxicity, myocardial damage, myocyte apoptosis, reduced contractility, and subsequent myocardial dysfunction (Lehrke & Marx, 2017; Schulze, Drosatos, & Goldberg, 2016; Seferovic, et al., 2018). Early studies in patients with obesity noted the accumulation of lipids around the epicardium, (Carpenter, 1962) a phenotype that was associated with cardiac dysfunction (Alpert, 2001; Carpenter, 1962). The link between lipid accumulation and heart failure is summarised in a recent review in the area(Schulze, et al., 2016). An improvement in cardiac metabolism and function in response to reduction in toxic lipids has been reported (I. J. Goldberg, Trent, & Schulze, 2012). Key evidence for this effect is summarised in the following sections.

Diabetes mellitus: Patients with type 2 DM (T2DM) have a two to three times increased risk of CV mortality compared to those without T2DM (Emerging Risk Factors, et al., 2015). CV mortality accounts for approximately 80% of deaths in patients with T2DM (M. Abdul-Ghani, Del Prato, Chilton, & DeFronzo, 2016). Data suggest that HF may lead to IR and DM (Amato, et

al., 1997; Swan, et al., 1997). DM and IR impairs the ability of the heart to adjust to changing energy demands by reducing the ability of the heart to use glucose and increasing the delivery of FA to the heart, thereby shifting cardiac metabolism towards a greater reliance on FA for energy(Bayeva, Sawicki, & Ardehali, 2013). In support of this observation, IR was found to be associated with myocardial triglyceride accumulation, cardiac remodeling and impaired diastolic function in overweight and obese women (Utz, et al., 2011). Greater dependence of the diabetic heart on FAO results in increased mitochondrial oxygen consumption in addition to increased cellular stress from elevated reactive oxygen species (ROS) production, and mitochondrial dysfunction (Dietl & Maack, 2017; Feuvray, 2010). These changes in myocardial metabolism may contribute to structural and functional alterations in the heart that can lead to progression of HF (Carley & Severson, 2005; Stanley, et al., 2005).

3. CURRENT THERAPIES AND THEIR EFFECTS ON CARDIAC METABOLISM

Current treatments for HF, aim at blocking neurohormonal signaling. However, more recently these therapies have been proposed to affect cardiac metabolism and associated energetics (Neubauer, 2007) (Figure 2A and 2B). The cardiac metabolic effects of some of the major HF therapies are described in the following sections.

β-blockers: β-adrenergic blockers are one of the main therapies that improve patient survival in HF. In these patients, long-term upregulation of catecholamines results in IR by antagonizing insulin, increasing lipolysis and raising free FA (FFA) levels (Nonogaki, 2000; Witteles & Fowler, 2008). Adrenergic blockade with carvedilol and metoprolol helps to improve myocardial function and survival in patients with HF through several mehanisms, including an energy-

sparing effect, possibly by favouring altered myocardial substrate utilization from FFA to glucose oxidation (Bayeva, et al., 2013; Eichhorn, et al., 1994; Wallhaus, et al., 2001). However, it is important to note the differences in the phramacological effects of various β-blockers on metabolism (Bayeva, et al., 2013).

Renin-angiotensin-aldosterone system (RAAS) inhibitors: The failing heart is associated with increased renin–angiotensin–aldosterone system activity (Mizuno, et al., 2001; Nakamura, et al., 2004; Yoshimura, et al., 2002). Prolonged activation of the RAAS system contributes to altered insulin/insulin-like growth factor 1 (IGF-1) signaling pathways and ROS formation, resulting in endothelial dysfunction and IR (Cooper, et al., 2007). Unlike β-blockers, ACEIs have been shown to increase FA uptake and improve myocardial energetics in HF. Studies in animal models with obesity and IR have shown that ACEIs can improve insulin responsiveness in the heart (Kadkhodayan, Coggan, & Peterson, 2013; Tabbi-Anneni, Buchanan, Cooksey, & Abel, 2008). Chronic ACE inhibition causes inactivation of bradykinin, which in turn has favorable effects on glucose uptake, glucose oxidation and glycolysis (Mori, Zhang, Oudit, & Lopaschuk, 2013). Furthermore, trials comparing the effects of ACEIs or ARBs with anti-hypertensive medicines have also demonstrated that RAAS blockade significantly improves insulin sensitivity (Grassi, et al., 2003; Jin & Pan, 2007; Olsen, et al., 2005). In-vitro studies with human adipocytes suggests that some ARBs can activate PPAR-γ target genes and induce adipogenesis (Janke, et al., 2006). As seen with ACEIs and ARBs, mineralocorticoid receptor antagonists can also increase glucose metabolism and restore insulin sensitivity (Pfeffer, et al., 2003; Yusuf, et al., 2000) (Vecchiola, Lagos, Carvajal, Baudrand, & Fardella, 2016).

Angiotensin receptor blocker-neprilysin inhibitors (ARNi): Sacubitril/valsartan (ARNi), acts by simultaneously blocking the RAAS and neprilysin (Ruilope, et al., 2010). Neprilysin degrades the peptides that have the potential to modulate lipid and glucose metabolism, such as natriuretic peptides (NPs), bradykinin, endothelin-1, and glucagon-like peptide 1 (GLP-1) (Standeven, et al., 2011). Neprilysin inhibition with sacubitril/valsartan increases the activity of NPs, bradykinin, GLP-1 and skeletal muscle cGMP, but decreases dipeptidyl peptidase 4 (DPP4) activity. Treatment with sacubitril/valsartan in normoglycemic patients with obesity and hypertension resulted in increased insulin sensitivity (Jordan, et al., 2017). A more recent study that compared the effects of sacubitril/valsartan with a comparator, amlodipine, demonstrated that sacubitril/valsartan did not elicit any clinically relevant changes in exercise-induced lipolysis or substrate oxidation in these patients with obesity and hypertension, suggesting that that the cardiovascular benefits of sacubitril/valsartan are not attributable to changes in lipid metabolism during exercise (Engeli, et al., 2018).

Natriuretic peptides (NPs): NPs can favorably affect human lipid metabolism by increasing lipolysis and insulin sensitization, while leptin release is suppressed (Birkenfeld, et al., 2012; Birkenfeld, et al., 2005; Birkenfeld, et al., 2008; Kerkela, Ulvila, & Magga, 2015; Moro, 2016; Schlueter, et al., 2014). NPs have been shown to improve energy production by enhancing mitochondrial biogenesis and oxidative capacity in skeletal muscle and adipose tissue (Bordicchia, et al., 2012; Engeli, et al., 2012; Kerkela, et al., 2015). In skeletal muscle, NPs can increase mitochondrial oxidative metabolism and lipid oxidation, thereby augmenting energy metabolism (Engeli, et al., 2012). ANP and BNP are potent mediators of lipolysis as compared with CNP that has a minor lipolytic effect (Sengenes, Berlan, De Glisezinski, Lafontan, &

Galitzky, 2000). In mice, transgenic BNP over-expression attenuates high-fat feeding-induced adiposity and IR (Miyashita, et al., 2009). Obesity and T2DM are associated with NP deficiency, thus suggesting a possible role of NPs in the pathophysiology of these diseases (Schlueter, et al., 2014). Finally, polymorphisms in the genes encoding atrial natriuretic peptide (ANP) and BNP contribute to the variability in the risk for T2DM (Jujic, et al., 2014; Meirhaeghe, et al., 2007). Previous studies have shown that ANP promotes adipose tissue lipolysis and hepatic ketogenesis (Birkenfeld, et al., 2008). The natriuretic system in adipose tissue is not desensitized in CHF. The lipolytic response to ANP is therefore preserved, ensuring that cardiac metabolism is maintained (Birkenfeld, Adams, Schroeder, Engeli, & Jordan, 2011).

NPs are degraded either through enzymatic degradation by neprilysin or via cellular uptake through the NP-C receptor. Evidence from various non-clinical and clinical studies has established the role of neprilysin inhibition in augmentation of the NP system (Doenst, et al., 2010; Jordan, et al., 2016; Kobalava, et al., 2016; Kuhn, 2016).

Recombinant ANP (carperitide) and BNP (nesiritide) were approved in 1995 and 2001 respectively for treatment of congestive HF. However, nesiritide was shown to be ineffective in reducing HF rehospitalization or death from any cause in the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure Trial (ASCEND-HF) (O'Connor, et al., 2011). Cenderitide, a chimeric peptide that activates natriuretic peptide receptor (NPR) A and NPRB, is being tested for preservation of left ventricular (LV) function in post-MI patients (Kerkela, et al., 2015).

Sodium glucose cotransporter (SGLT) inhibitors: SGLT inhibtiors belong to a class of drugs that inhibit glucose reabsorption in the kidney, thereby increasing urinary glucose excretion and

providing an important therapeutic strategy for the treatment of T2DM (M. A. Abdul-Ghani, Norton, & Defronzo, 2011). Among the two most well known SGLTs, 90% of glucose reabsorption is *via* SGLT-2 and the remaining 10% is *via* SGLT1(Hediger & Rhoads, 1994). Dapagliflozin (List, Woo, Morales, Tang, & Fiedorek, 2009), empagliflozin (Grempler, et al., 2012) and canagliflozin (Neal, et al., 2017) are recently developed selective SGLT-2 inhibitors that have been investigated for the treatment of T2DM.

An earlier study that evaluated the efficacy and safety of dapagliflozin in patients with T2DM and pre-existing cardiovascular disease (CVD), showed that dapagliflozin significantly reduced haemoglobin A_{1c} (HbA_{1c}) (−0.38% [−4.2 mmol/mol]), body weight and systolic blood pressure without adversely affecting CV safety relative to placebo (Cefalu, et al., 2015). Another recent study, the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients study (EMPA-REG OUTCOME), has shown that treatment with SGLT-2 inhibitor empagliflozin has beneficial cardio-metabolic effects in patients with T2DM and established CVD. A 14% reduction in primary major adverse cardiac events was observed in addition to a 35% reduction in HF hospitalizations (Zinman, et al., 2015).

The results of the EMPA-REG trial have been validated from the CANVAS program (Neal, et al., 2017). CANVAS indicated that canagliflozin reduces CV events by 14%, and the rate of renal decline by 40%, although at an increased risk of lower-limb amputation and bone fractures. Clinical practice guidelines have already begun to reflect the efficacy of SGLT-2 inhibitors in this group of patients and will impact on clinical decision making in cardiologists (Ponikowski, et al., 2016; Tanaka & Node, 2017).

Finally, SGLT-2 inhibitors increase ketone body availability by increasing FAO in the liver via β-oxidation. Indeed, a recent untargeted metabolomic study showed an increase in the levels of ketone bodies as well as branched chain amino acids in patients with T2DM and CV disease treated with empagliflozin (Kappel, et al., 2017). Ketone bodies (acetoacetate and β-hydroxybutyrate) are then exported from the liver into blood stream and are utilized by the heart in preference to FA, resulting in more efficient oxidation and increase ATP hydrolysis to produce energy (Ferrannini, et al., 2016). Moreover, treatment with SGLT-2 inhibitors also increases haematocrit and erythropoietin, possibly improving oxygen delivery to tissues and organs (Ferrannini, et al., 2017; Ferrannini, et al., 2016; Lambers Heerspink, de Zeeuw, Wie, Leslie, & List, 2013).

Glucagon-like peptide-1 (GLP-1) receptor agonists:

GLP-1 receptors are expressed in the endothelium and cardiac and vascular myocytes. GLP-1 administration in isolated mouse heart showed cardioprotective effects by increasing glucose uptake, cAMP and cGMP release, left ventricular developed pressure, and coronary flow (Ban, et al., 2008). Lixisenatide, a GLP-1 receptor agonist was shown to be safe in patients with diabetes and acute coronary syndrome (ACS) in ELIXA trial (Pfeffer, et al., 2015). The long-acting liraglutide and very-long-acting semaglutide demonstrated superiority over placebo in reducing the occurence of CV events in high-risk patients with diabetes in LEADER and SUSTAIN-6 trials, respectively (Marso, Bain, et al., 2016; Marso, Daniels, et al., 2016) . Furthermore, a non-significant reduction in HF hospitalizations was observed in liraglutide treatment (Margulies, et

al., 2016). However, liraglutide treatment did not improve clinical outcomes in HFrEF patients with or without diabetes (Jorsal, et al., 2017).

4. RELEVANCE FOR CLINICAL PRACTICE – TARGETING DYSREGULATED METABOLIC PATHWAYS IN HEART FAILURE

4.1 Optimizing myocardial substrate utilization – glycolysis and FA metabolism

Several therapeutic strategies to optimize myocardial substrate utilization in HF have been investigated suggesting that metabolic therapy may be an important therapeutic option (Rosano, Vitale, & Spoletini, 2015). **Table 1** summarizes the studies of cardiac metabolism modulators and their clinical benefits.

Fatty acid oxidation inhibitors: Reversal of the metabolic 'foetal reprogramming' that is characteristic of HF would aim to metabolise substrates as quickly as possible using the available oxygen. However, it is not desirable to depend on FAO under HF conditions in which oxygen demands are increased and supply limited. There is a risk of lipotoxicity and the oxidative capacity of the cardiomyocytes is also limited (due to reduced mitochondrial mass). An alternative approach would be to block FAO to stimulate the heart to switch to glucose oxidation (Heggermont, Papageorgiou, Heymans, & van Bilsen, 2016). In support of this approach, postinfarction HF was associated with upregulation of the glucose transporter, GLUT-1 in rats, while GLUT-1 overexpression prevented the developement of HF in a mouse model (Liao, et al., 2002; Rosenblatt-Velin, Montessuit, Papageorgiou, Terrand, & Lerch, 2001). Etomoxir and perhexiline are inhibitors of CPT-1, which also block FAO. They decrease the activity of this rate-limiting enzyme in FAO pathway, while favoring glucose oxidation (*via* the Randle Cycle)

(Lam & Lopaschuk, 2007). Studies with etomoxir have shown that it can improve cardiac function by enhancing sarcoplasmic Ca^{2+} handling and increasing sarco/endoplasmic reticulum Ca2+-ATPase (SERCA)2A (Rupp & Vetter, 2000; Zarain-Herzberg, Rupp, Elimban, & Dhalla, 1996). However, its association with serious side effects (including hepatotoxicity caused by increased liver transaminase levels) means that etomoxir is not considered a suitable therapy for use in HF patients (Holubarsch, et al., 2007).

Perhexiline is an anti-anginal drug that inhibits the cardiac, but not hepatic isoform of CPT-1 and is associated with improved exercise capacity and left ventricular ejection fraction (LVEF) in patients with HF (Lee, et al., 2005). Trimetazidine (TMZ) is a second anti-anginal agent, which has been approved world-wide (in many European countries) (Beadle & Frenneaux, 2010). It has anti-ischemic actions without causing central hemodynamic effects. TMZ belongs to a group of inhibitors known as 'partial fatty-acid oxidation' (PFox) inhibitors (Fragasso, et al., 2006). It exerts its effects by causing a shift in cardiac energy metabolism to glucose metabolism. The response results in a greater production of high-energy phosphates (increase in cardiac phosphocreatinine: ATP ratio by 33%) (Fragasso, et al., 2006) and causes an anti-ischemic effect. In addition, TMZ is known to cause an improvement in endothelial function, a reduction in calcium overload and free radical-induced injury (improved reperfusion mechanical function), (Fragasso, et al., 2003; Gambert, et al., 2006) and an inhibition of cell apoptosis and cardiac fibrosis (L. Zhang, et al., 2016) There is a growing evidence to support the efficacy of TMZ in improving LV function, cardiac volume, contractility, inflammation, endothelial function and fasting glucose levels (Rosano, et al., 2015).

Ranolazine is an inhibitor that is similar in structure and function to TMZ (also a PFox inhibitor). It acts by blocking FAO to enhance glucose oxidation, thus indirectly increasing PDH complex activity, and resulting in increased ATP production (McCormack, Barr, Wolff, & Lopaschuk, 1996). It is currently approved as an anti-anginal agent in Europe and the USA. It has been shown to inhibit the late sodium current and normalize Ca^{2+} elimination in cardiac myocytes in end-stage HF, thus improving myocardial diastolic function and reducing diastolic wall tension (Sossalla, et al., 2008). Furthermore, ranolazine has been shown to significantly increase LVEF in patients with systolic and diastolic HF (Horvath & Bers, 2014).

The RAnoLazine for the Treatment of Diastolic Heart Failure study (RALI-DHF) was a randomized, prospective, placebo-controlled study in diastolic HF patients (ranolazine=12; placebo=8) with ejection fraction (EF) ≥45%. The study concluded that ranolazine improves haemodynamic measurements (reduction in LV end-diastolic pressure and pulmonary capillary wedge pressure) in patients with HF. However, no significant effects on relaxation parameters or BNP concentrations were observed (Maier, et al., 2013).

Peroxisome proliferator-activated receptor agonists (PPARs): PPARs play a role in the modulation of glucose homeostasis, IR and blood pressure (Desvergne & Wahli, 1999; Willson, Lambert, & Kliewer, 2001). PPARα agonists, such as fibrates, mediate the hypolipidaemic action of the thiazolidinediones (TZDs), while the PPARγ agonists act as receptors for these glitazones (Barbier, et al., 2002). PPARs decrease the circulating FFA supply to the heart, resulting in reduced cardiac FAO rates (Lopaschuk, et al., 2010). A systematic review concluded that fibrates lower the risk of major CV and coronary events compared with placebo, but do not affect the risk

of CV or all-cause mortality or prevent the development of HF (Jun, et al., 2010). PPARγ agonists, TZDs (rosiglitazone and pioglitazone), are used to treat patients with T2DM. A systematic study analysed the CV outcomes in patients with T2DM using TZDs, concluded that rosiglitazone is associated with a higher risk of congestive HF, myocardial infarction (MI), and death than pioglitazone (Loke, Kwok, & Singh, 2011). TZDs affect lipid metabolism, and cause a significant increase in triglyceride and low density lipoprotein cholesterol levels. This effect was greater with rosiglitazone than with pioglitazone (R. B. Goldberg, et al., 2005). Furthermore, rosiglitazone, exhibited a more powerful renal PPARγ agonistic effect, leading to more fluid retention, a worsening of HF, and an increased in HF-associated hospitalizations (Loke, et al., 2011; H. Zhang, et al., 2005).

4.2 Ketone bodies

Ketone bodies are an alternative and glucose-sparing fuel source, which are frequently oxidized in the heart and skeletal muscle. Studies in both animal models (Aubert, et al., 2016) and humans (Bedi, et al., 2016), have demonstrated that ketone utilization is increased in HF. These are in contrast to the more recent observation that increased levels of ketone bodies may lead to contractile dysfunction (Taegtmeyer, 2017). Ferrannini et al pointed to the hypothesis that β-hydroxybutyrate is freely taken up by the heart during persistent, but mild hyperketonemia (such as that seen during treatment with SGLT-2 inhibitors) and utlized in preferance to FAs. (Ferrannini, et al., 2016). Such a mechanism may provide some explanation for the cardioprotection observed in the EMPA-REG study (Zinman, et al., 2015). While these studies have already been discussed in detail in the section on ketone metabolism (section 2.2), they suggest an ongoing debate surrounding the role of ketone bodies in HF. Recent studies suggest

that ketone oxidation may be a key metabolic adaptation in human HF , implying that reducing ketone utilization may be a valuable therapeutic approach (Kappel, et al., 2017; Wende, et al., 2017). However, further studies are required to fully uncover the effect of chronic ketone utilization on cardiac metabolism and function.

4.3 Purinergic signaling

Several studies have assessed the effects of modulators of purinergic signaling on cardiac metabolism. Dipyridamole (DIP) is an adenosine uptake blocker that causes increased adenosine levels (Stea, et al., 2016). Small observational studies in patients with HF have shown that DIP improves LV function, symptoms (New York Heart Association [NYHA] class) and exercise capacity (Akhtar, Ordovas, Martin, Higgins, & Michaels, 2007; Sanada, et al., 2007). Rolofylline is an adenosine A_1 receptor antagonist that increased diuresis in patients with AHF (Givertz, et al., 2007) and significantly increased GFR and renal plasma flow in CHF (Givertz, et al., 2007). This suggests that rolofylline may have potential for the clinical treatment of renal dysfunction in HF.

In a dose-ranging pilot study in 301 patients with AHF, rolofylline demonstrated short and medium-term clinical benefits in association with renal protection (Cotter, et al., 2008). However, the results from the pivotal study, PROTECT (A Placebo-controlled Randomized Study of the Selective A_1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized With Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function) did not demonstrate a renal-protective effect in 2033 patients admitted with acute decompensated heart failure (ADHF) and renal dysfunction, despite similarities in study design, inclusion criteria, and dose of rolofylline in the pilot study (Massie,

et al., 2010). The authors concluded that the inconsistency in study results could be due to the complexity and heterogeneity of AHF and suggested that new therapeutic approaches are needed. Similar to PROTECT, the REACH UP study did not demonstrate any CV benefit with rolofylline in patients with acute decompensated HF and worsening renal function (Gottlieb, et al., 2011).

The Acute Myocardial Infarction STudy of ADenosine (AMISTAD) trial (Mahaffey, et al., 1999) and AMISTAD II (Ross, et al., 2005) studied the effect of adenosine on infarct size in MI patients. While a significant reduction in infarct size was reported following adenosine treatment in AMISTAD (patients within 6 h of an onset of MI), this effect could not be replicated in AMISTAD II, in which infarct size was assessed in ST-segment elevation in MI patients undergoing reperfusion therapy. The authors noted that infarct size was reduced in patients receiving a higher concentration of adenosine (70-µg/kg/min infusion). suggesting that a larger study at the 70-µg/kg/min dose is warranted.

AICA-riboside, otherwise known as acadesine, acts by increasing the adenosine bioavailability. By activating the 5' adenosine monophosphate pathway, it increases the ATP production. However, development of acadesine was terminated after an analysis that suggested the drug had a low probability of reducing cardiovascular events in patients who underwent coronary artery bypass surgery (CABG) (NCT00872001).

5. CONCLUSION

Shifting myocardial energetics from FAO to favor more energy-efficient metabolic pathways have the potential to improve cardiac function and prognosis in HF. Furthermore, the use of insulin-sensitizing agents may promote the ability of glucose to be utilized as a preferred metabolic substrate in HF. Given that current HF therapies and/concepts, including purinergic signaling are known to have effects on metabolic pathways, agents that leverage more efficient myocardial energetics should be further investigated.

In the future, it is hoped that HF patients will not only be stratified according to their LVEF and any associated co-morbidities, but also according to their individual metabolic status allowing personalized metabolic treatment for each patient that is tailored to their specific metabolic needs.

TABLE 1: Clinical studies using metabolic modulators

Metabolic modulator	Metabolic mechanism affected by modulator	Study type (pre-clinical studies, POC studies, pilot studies and clinical trials)*
β-blockers		
Non-vasodilators	↓ insulin sensitivity ↑ glucose levels Neutral/negative effect on lipid metabolism	Prospective study; ARIC (n=12,550)(Gress, Nieto, Shahar, Wofford, & Brancati, 2000) Double-blind, prospective, parallel-group study; LIFE (n=8,300)(Dahlof, et al., 2002) Prospective, randomized, open-blinded study; INVEST (n=22,576)(Pepine, et al., 2003) Prospective, randomized, open-blinded study; ASCOT-BLA (n=19,257) (Gupta, et al., 2008)
Vasodilators		
Carvedilol	↓ FFA metabolism	
Carvedilol/metoprolol		Pilot study (n=9)(Wallhaus, et al., 2001)
Talinolol/atenolol		Double-blind, randomized study (n=72)(Jacob, et al., 1996) Double-blind, randomized study; TALIP (n=198)(Sourgens, Schmidt, & Derendorf, 2003)
Carvedilol/bisoprolol	↑ glucose metabolism	Randomized study (n=26)(Podbregar & Voga, 2002)
ACE inhibitors		
Captopril	↑ insulin sensitivity	*In vivo* study in ob/ob mice(Tabbi-Anneni, et al., 2008)
Ramipril	↑ insulin sensitivity	Double-blind, randomized Heart Outcomes Prevention Evaluation study (n=9297)(Yusuf, et al., 2000)
ARBs		
Candesartan	↑ glucose metabolism	Parallel, randomized, double-blind, controlled trials; CHARM-Overall program (n=7601)(Pfeffer, et al., 2003)
SGLT-2 inhibitors		
Canagliflozin	↑ glucose metabolism/excretion	Randomized, double-blind, placebo-controlled trials; CANVAS program (n=10,142)(Neal, et al., 2017)
Empagliflozin	↑ glucose metabolism/excretion	Randomized, double-blind, placebo-controlled trial (EMPA-REG; n=7020)(Zinman, et al., 2015)
Dapagliflozin	↑ glucose metabolism/excretion	Randomized, placebo-controlled, double-blind trial (n=75)(Lambers Heerspink, et al., 2013)
GLP-1receptor agonists		
Lixisenatide	Inhibit glucagon secretion ↑ insulin secretion	Randomized, double-blind, placebo-controlled trial (ELIXA; n=6068)(Pfeffer, et al., 2015)
Liraglutide	Inhibit glucagon secretion ↑ insulin secretion	Randomized , double-blind, placebo-controlled trial (LEADER; n=9340)(Marso, Daniels, et al., 2016)
Semaglutide	Inhibit glucagon secretion ↑ insulin secretion	Randomized , double-blind, placebo-controlled trial (SUSTAIN-6; n= 3297) (Marso, Bain, et al., 2016)

CPT-1 inhibitors		
Etomoxir	↓ FFA metabolism	*In-vivo* rat model(Zarain-Herzberg, et al., 1996) Randomized, double-blind study; ERGO (n=350)(Holubarsch, et al., 2007)
Perhexiline	↓ FFA metabolism	*In-vivo* rat model (Rupp & Vetter, 2000) Randomized, double-blind, placebo-controlled, parallel-group study (n=50)(Beadle, et al., 2015) Randomized, double-blind study (n=56)(Lee, et al., 2005) Randomized, double-blind, placebo-controlled study (n=72)(Singh, et al., 2014)
Other anti-anginal agents		
Trimetazidine	↓ FFA metabolism	*Ex vivo* rat model(Gambert, et al., 2006) *In vivo* rat model(L. Zhang, et al., 2016) Randomized open-label study (n=55)(Fragasso, et al., 2006) Randomized, double-blind, crossover study (n=16)(Fragasso, et al., 2003) Double-blind parallel group study (n=149)(Detry, et al., 1994)
Ranolazine	↑ glucose metabolism	*Ex vivo* rat model(McCormack, et al., 1996) *Ex vivo* explant model (n=14)(Sossalla, et al., 2008) Double-blind, placebo-controlled, randomized study, (MERLIN)-TIMI 36 (n=6560)(Morrow, et al., 2007) Randomized, double-blind, placebo-controlled POC study; RALI-DHF (n=20)(Maier, et al., 2013)
PPAR agonists		
Fibrates	↓ triglycerides	Systemic review & meta-analysis(Jun, et al., 2010)*
Thiazolidinediones	↑ insulin sensitivity	Systemic review & meta-analysis(Loke, et al., 2011)*
Pioglitazone		Randomized controlled trial (n=802)(R. B. Goldberg, et al., 2005) Randomized, double-blind, double-dummy with active comparator, intervention; PIRAMID (n=78)(van der Meer, et al., 2009)
ARNi		
Sacubitril/valsartan	↑ insulin sensitivity ↑ abdominal adipose lipolysis (NS) No change in whole body lipolysis and in exercise induced lipolysis	Randomized, double-blind, double-dummy, active-controlled, and parallel-group (n=98)(Engeli, et al., 2018; Jordan, et al., 2016)
Natriuretic peptides	↑ fatty acids	Human physiological study (n=14)(Birkenfeld, et al., 2005)
	↑ lipolysis	Cross-over study (n=10)(Birkenfeld, et al., 2006)
	↑ postprandial energy expenditure	Randomized, double-blind, cross-over study (n=12)(Birkenfeld, et al., 2008)
	↑ adiponectin	Human physiological study (n=12)(Birkenfeld, et al., 2012)
	↑ adiponectin	Human physiological study (n=47)(Yamaji, et al., 2009)
	↓ ghrelin (induced by BNP)	Randomized, placebo-controlled, crossover, single-blinded

		study (n=10)(Vila, et al., 2012)
Ketone bodies	↑ β-hydroxybutyrate dehydrogenase-1 causing increased delivery and uptake of ketone bodies	*In vivo* mouse model(Aubert, et al., 2016) *Ex vivo* explant model (n=35)(Bedi, et al., 2016)
Purinergic signaling		
Dipyridamole	↓ adenosine uptake and ↑ diuretic responsiveness	Pilot study (n=6)(Akhtar, et al., 2007) Prospective, open, randomized, controlled trial (n=28)(Sanada, et al., 2007)
Rolofylline	Adenosine A1 receptor antagonist. ↑ diuretic responsiveness	Randomized, double-blind, placebo-controlled, POC (n=146)(Givertz, et al., 2007) Randomized, double-blind, placebo-controlled, two-way crossover study (n=32)(Givertz, et al., 2007) Pilot: PROTECT−randomized, placebo-controlled, dose-finding study (n=301)(Cotter, et al., 2008) Double-blind, placebo-controlled study (n=2033)(Massie, et al., 2010) REACH UP study− randomized, double-blind, placebo-controlled (n=76)(Gottlieb, et al., 2011)
Adenosine		Prospective, open-label, placebo controlled, randomized study; AMISTAD (n=236)(Mahaffey, et al., 1999) Double-blind, placebo-controlled, randomized study; AMISTAD-II (n=2,118)(Ross, et al., 2005)
L-carnitine	↑ glucose metabolism	*Ex vivo* rat model (Broderick, Quinney, Barker, & Lopaschuk, 1993)

*Systematic review and meta-analysis

Abbreviations: ACEi, angiotensin converting enzyme inhibitors; AMISTAD, Acute Myocardial Infarction STudy of Adenosine; ARB, angiotensin II receptor blockers; ARIC, Atherosclerosis Risk In Communities; ARNI, angiotensin receptor blocker–neprilysin inhibitor; ASCOT-BPLA, Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm; BNP, B-type natriuretic peptide; CANVAS Program, The Canagliflozin Cardiovascular Assessment Study and CANVAS-Renal; CHARM, Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity; EMPA-REG, Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial; ERGO, etomoxir for the recovery of glucose oxidation; FFA, free fatty acid; INVEST, International Verapamil-Trandolapril Study; LIFE, Losartan Intervention for Endpoint Reduction; MERLIN-TIMI 36, Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes; PIRAMID, Influence on tRiglyceride Accumulation in the Myocardium in Diabetes; POC, proof of concept; PPAR, Peroxisome proliferator-activated receptor; PROTECT, Placebo-Controlled Randomized Study of the Selective A(1) Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized With Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function; SGLTi, sodium glucose cotransporter inhibitors

Figure legends

Figure 1: Pathological changes in the healthy heart leading to insulin resistance (IR) and the development of heart failure. Mechanical dysfunction and other associated co-morbidities (obesity, diabetes, and metabolic syndrome) can lead to IR. Increased insulin levels lead to metabolic disturbances in adipose tissue, liver, and skeletal muscle. Metabolic perturbations in these systems can subsequently promote the progression to heart failure.

Figure 2A: Overview of major targets of metabolic modulators. Several metabolic modulators exert their effects on cardiac metabolism indirectly through effects on other organs and cell types (adipose tissue, platelets, endothelial cells, or erythrocytes).

Figure 2B: Summary of metabolic pathways and therapies that modulate cardiac metabolism. Natriuretic peptides (ANP and BNP) favor lipolysis and result in an increase in free fatty acids. Fatty acids are taken up by the liver and undergo β-oxidation to form ketone bodies (acetoacetate and β-hydroxybutyrate). The ketones are transferred to the heart via the bloodstream. In the cardiomyocyte, the ketone bodies enter the Krebs cycle and undergo oxidative phosphorylation. In cardiomyocytes, acetyl-CoA formed from the ketones limits additional production of acetyl-CoA from the pyruvate and β-oxidation pathways (dotted arrows).

Conflicts of Interest Statement

[Financial interests unrelated to primary employment and conflicts of interest]

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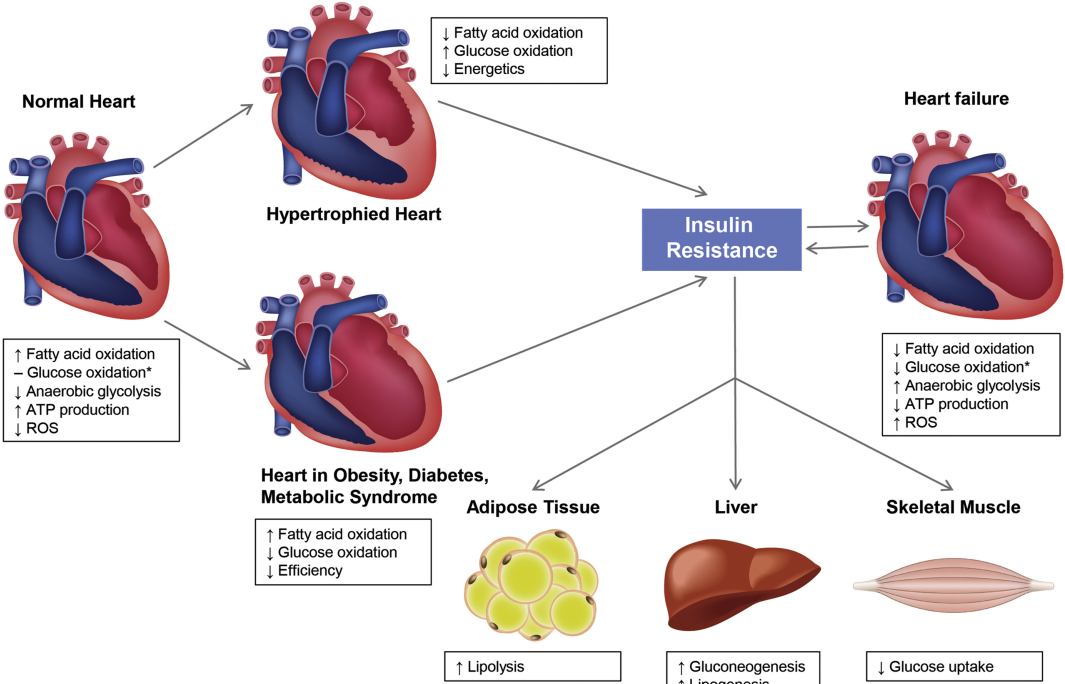
Metabolic remodelling and the development of heart failure



ATP - Adenosine Tri-Phosphate; ROS – reactive oxygen species; VLDL – very low density lipoprotein

* An initial increase in glucose oxidation is seen in the early stages of heart failure, which is then reduced in advanced heart failure.

Figure 1

Metabolic modulators and their targets

CPT-1 inhibitors *(etomoxir, perhexiline)*
FAO inhibitors

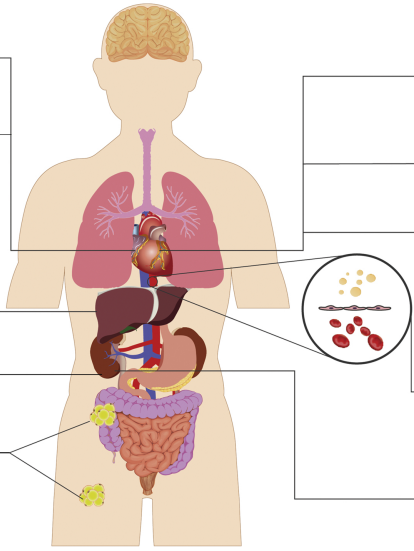
Other anti-anginal agents
(ranolazine, trimetazidine)
FAO inhibitors

Ketone bodies
Produced in the liver and transferred to the heart. Proposed to act as superfuel

SGLT2 inhibitors
(empagliflozin, dapagliflozin)
Blocks SGLT2 in the kidney to increase glucose excretion

Natriuretic peptides
Favour lipolysis of adipose tissue (visceral and subcutaneous) to produce fatty acids for FAO.

ARNi
(sacubitril/valsartan)
Lipid and glucose modulator



ACEi
(captopril, ramipril)
Circulating fatty acid modulators

PPAR agonists:
(fibrates, thiazolidinediones)
Circulating fatty acid modulators

β-blockers
(non-vasodilators, vasodilators)
Circulating fatty acid and glycolysis modulators

Dipyridamole
Purinergic signaling (inhibits adenosine uptake in platelets, endothelial cells and erythrocytes)

Rolofylline
Purinergic signaling (adenosine A1 receptor antagonist and diuretic)

Figure 2A

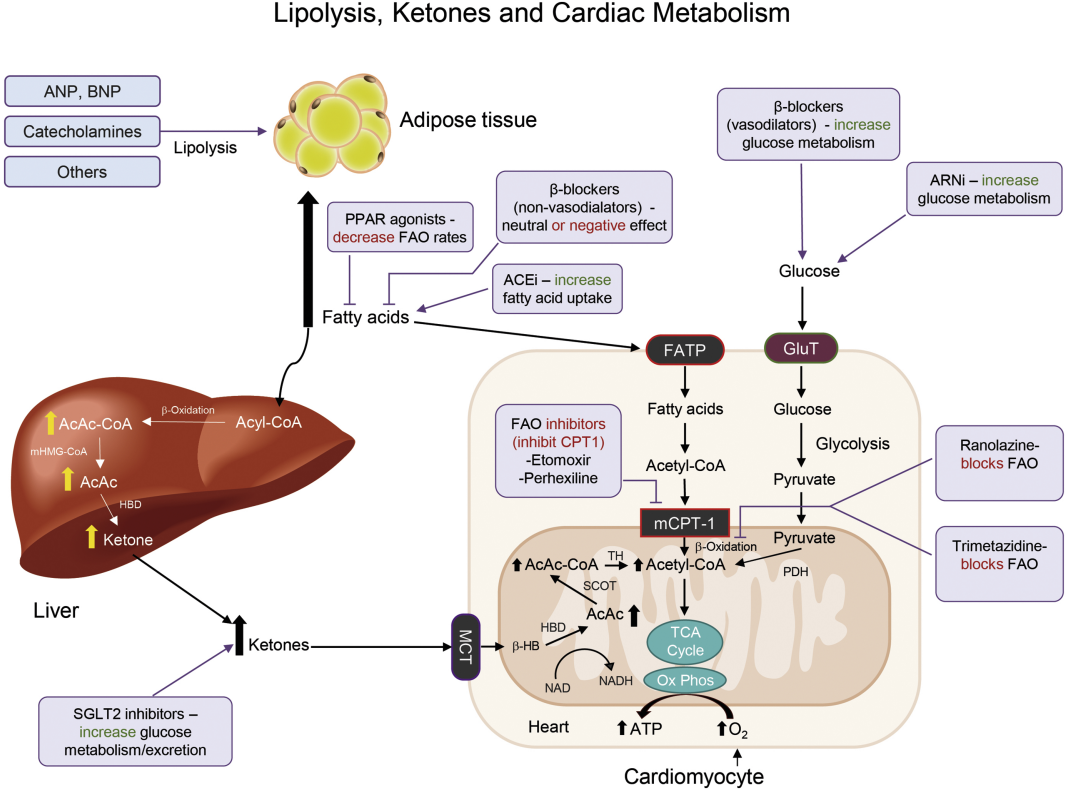

Lipolysis, Ketones and Cardiac Metabolism
ANP, BNP
Catecholamines
Others
Lipolysis
Adipose tissue
β-blockers (vasodilators) - increase glucose metabolism
ARNi – increase glucose metabolism
β-blockers (non-vasodialators) - neutral or negative effect
PPAR agonists - decrease FAO rates
ACEi – increase fatty acid uptake
Fatty acids
Glucose
FATP
GluT
Fatty acids
Glucose
Glycolysis
Acetyl-CoA
Pyruvate
FAO inhibitors (inhibit CPT1) -Etomoxir -Perhexiline
Ranolazine- blocks FAO
Trimetazidine- blocks FAO
mCPT-1
Pyruvate
β-Oxidation
TH
PDH
AcAc-CoA
Acetyl-CoA
SCOT
AcAc
HBD
β-HB
TCA Cycle
NAD
NADH
Ox Phos
Heart
ATP
O2
Cardiomyocyte
AcAc-CoA
β-Oxidation
Acyl-CoA
mHMG-CoA
AcAc
HBD
Ketone
Liver
Ketones
MCT
SGLT2 inhibitors – increase glucose metabolism/excretion

Figure 2B